REMARKS

Applicants are amending the application to add new claims 47 to 54. Basis for the newly added claims 47 to 54 is found, for example, in the claims as originally filed as well as in the specification in the Summary of the Invention on page 2, line 29 to page 3, line 6, page 13, lines 1 to 29, and on page 15, lines 6 to page 17, line 4. Upon entry of the amendment, claims 7, 8, 10 -19, and 47 to 54 remain pending.

Newly added claims 47 to 54 are directed to methods of treating a patient having chronic HCV infection with a therapeutically effective amount of a combination therapy of pegylated interferon-alfa and ribavirin to substantially lower HCV-RNA in association with a therapeutically effective amount of Vitamin E and Vitamin C to ameliorate ribavirin-related hemolysis. Thus, applicants' claimed invention, as amended, provides an improved HCV therapy by ameloriating the ribavirin-related hemolysis throughout the duration of the combination therapy especially in the first 4 to 12 weeks, of therapy so as to produce a sustained virological response in more patients than previously possible.

McHutchinson et al., David et al., Poynard et al., and Reichard et al. each teach the use of interferon a-2b in combination with ribavirin to treat HCV. These four references fail to teach use of antioxidants much less the specific combination therapy of pegylated interferon-alfa and ribavirin in asociation with the specific combination of the two antioxidants, Vitamin E and Vitamin C, to treat ribavirin-induced hemolysis. Only ribavirin dose reduction is taught.

None of the deficiencies of these four references are cured by Abella et al. which discloses the evaluation of the antioxidant activity of Vitamin E in the plasma of healthy volunteers to which an oxygen free radical initiator ("AAPH") was added. Nowhere in Abella et al. is there any teaching about treating HCV patients or ribavirin -induced anemia, much less any suggestion that the combination of Vitamin E with Vitamin C would be useful in treating ribavirin –induced hemolysis in HCV patients being treated with the ribavirin-interferon alfa combination therapy. Applicants have discovered that ribavirin –induced hemolysis in HCV patients being treated with only Vitamin E and the ribavirin-interferon alfa combination therapy is **not significantly better** than ribavirin –induced hemolysis in HCV patients being treated with the ribavirin-interferon alfa combination therapy-in the absence of Vitamin E. Applicants assert that there is no motivation in the references alone or in combination to make the modification needed to bridge the gap to

the claimed invention. The combined teachings of the references do not suggest the claimed invention, as amended, which specifies that a combination of two antioxidants in association with ribavirin and interferon-alfa be used to treat HCV. Only by hindsight reconstruction using applicants' claimed invention as a template can the gap from the prior art to the claimed invention be bridged.

Reference is now made to U.S. Patent 4917888 (Katre et al., 1990 and ", The '888 patent").

The '888 patent discloses various pegylated proteins but cures none of the deficiencies in McHutchison, et al., Davis, et al., Poynard, et al., Reichard, et al., or Abella et al., alone or in combination.

None of these six references, alone or in combination teach use of the combination of Vitamin E with Vitamin C in association with the ribavirin-interferon alfa, or the ribavirin-pegylated interferon alfa combination therapy to treat HCV more effectively by ameloriating the ribavirin-induced hemolysis.

Applicants assert that the claimed invention, as amended, is in statutory compliance with 35 U.S.C § 103.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

January 22, 2003
Date of Deposit

THOMAS D. HOFFMAN
Registered Representative

Signature

01/22/2003
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APPENDIX

47. A method of treating a patient having chronic HCV infection which comprises administering to said patient a therapeutically effective amount of a combination therapy of pegylated interferon-alfa and ribavirin for a time sufficient to substantially lower HCV-RNA in association with a therapeutically effective amount of Vitamin E and Vitamin C for a time sufficient to ameliorate ribavirin-related hemolysis.
48. The method of claim 47 wherein the pegylated interferon alfa is pegylated interferon alfa-2a.
49. The method of claim 47 wherein the pegylated interferon alfa is pegylated interferon alfa-2b.
50. The method of claim 47 wherein the time for administering the combination therapy in association with the therapeutically effective amount of Vitamin E and Vitamin C and is a period of at least about 24 weeks.
51. The method of claim 47 wherein the time for administering the combination therapy in association with the therapeutically effective amount of Vitamin E and Vitamin C and is a period of at least about 48 weeks.
52. A method of treating a patient having a chronic HCV infection which comprises administering to said patient for a time period of at least about 24 weeks a therapeutically effective amount of a combination therapy of pegylated interferon alfa and ribavirin sufficient to lower detectable HCV-RNA in association with a therapeutically effective amount of Vitamin E and Vitamin C sufficient to ameliorate ribavirin-related hemolysis.

infection.

54. The method of claim 52 wherein the patient has a HCV genotype 1 infection, 53. The method of claim 52 wherein the patient has a HCV genotype 2 or 3 and the time period is about 48 weeks.